REMARKS

Applicant respectfully requests reconsideration. Claims 90, 93, 96, 98-101, 104, 133-142, 144-146 and 149-151 were previously pending in this application. No claims are amended. As a result, claims 90, 93, 96, 98-101, 104, 133-142, 144-146 and 149-151 are still pending for examination with claim 104 being an independent claim. No new matter has been added.

Information Disclosure Statement

Applicants enclose herewith two Information Disclosure Statements with Form 1449. The first Information Disclosure Statement with Form 1449 is a resubmission of references previously forwarded to the Examiner but not considered by the Examiner. Applicants hereby reiterate the request for the Examiner to review each of the references on the list. Applicants previously enclosed copies of the references with a prior Information Disclosure Statements or in a parent patent application. Thus it is believed that an additional copy of the references is not required. The second Information Disclosure Statement provides references not previously submitted to the Patent Office. Where it is required, copies of the references are enclosed.

Rejection Under 35 U.S.C. 112

Claims 133, 135, 137 and 193 remain rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement.

According to the Examiner the incorporation by reference will not be perfected until Applicant provides a statement that the material being inserted is the material previously incorporated by reference and contains no new matter. Applicant hereby states that the limitation "wherein the CpG oligonucleotide does not include a GCG trinucleotide at a 5' and/or 3'terminal of the oligonucleotide" added into the specification is the material previously incorporated by reference. The amendment contains no new matter.

Claims 90, 93, 96, 98-101, 104, 133-142, 144-146 and 149-151 remain rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement.

Pages 19-30 of the Office Action dated September 12, 2007 repeat the entire enablement rejection found in the prior Office Action. Applicant hereby specifically reiterates each of the arguments set forth in the Response to Office Action dated January 4, 2007. Since the Examiner included the prior rejection in the Office Action, Applicants reiterate prior arguments at the end of this section.

Pages 4-19 of the Office Action address the Examiner's reasons for maintaining the rejection for lack of enablement. Each of these issues is addressed herein.

a. undue experimentation

The Examiner has addressed Applicants point regarding undue experimentation. Specifically the Examiner has stated that the Office does not have to specify the type of undue experimentation. Applicants agree that determination of undue experimentation is based on a Wands analysis. However, in the Office Action the Examiner has concluded that a skilled artisan would have to undertake experimentation with respect to many parameters involved with the claimed invention and further that all Applicant has provided is an "association study". The point that Applicant has previously made is that data was included in the patent application as filed and that such data would be sufficient to one of ordinary skill in the art to support a finding that CpG oligonucleotides would be useful for the treatment of bacterial infection. Applicants stated in the specification that the CpG oligonucleotides, which Applicant describes structurally, would be useful to treat bacterial infection. In order to practice the claimed invention one of skill in the art would simply need to administer the CpG oligonucleotides to treat the bacterial infection. Unless the utility of the invention is being challenged, it is unclear why the methods would require undue experimentation. One of skill in the art would not need to experiment with immuno modulation, cytokine production and how it relates to bacterial infection, as suggested by the Examiner. One of skill in the art would not need to understand the mechanism. Applicant has provided the compound and presented a credible use for that compound in the treatment bacterial infection. Applicant's data would have been accepted by those skilled in the arts at the time the application was filed, thus providing a credible utility.

The Examiner states on page 6 that Applicant has not supported an "assertion of predictability with any evidence that commensurate with the claimed invention, a method of treating bacterial infection with the administration of CpG oligonucleotides." The Examiner further states that the discovery that CpG oligonucleotides stimulate a potent immune response "does not commensurate or equate to a method of treating bacterial infection." On pages 7-8 it is stated that Applicants have not provided evidence that the immune stimulation described in the specification for CpG oligonucleotides would be sufficient to establish that CpG oligonucleotides are useful for treating bacterial infection. In response, Applicants summarize the following three references which were published close to the time of filing of the patent application. Each of the references relates to the role of various cytokines in the treatment of bacterial infection. The three references establish that in 1994 one of ordinary skill in the art accepted that in vivo cytokine induction was sufficient to treat bacterial infection.

Totte et al., Infection and Immunity, June 1994, v. 62, p. 2600-2604, is a study in cows demonstrating that IFN-α produced in vivo in response to infection by the *rickettsia cowdria ruminatium* slows down the course of the infection and allows the animals to mount a protective immune response. The IFN-α produced by the bacterial infection in vivo is similar to the cytokine response observed by CpG oligonucleotides. As described in the specification, on for instance page 42, it is believed that CpG oligonucleotides mimic bacterial infection resulting in the production of an endogenous immune response by the host that is useful for treating the infection. CpG oligonucleotides are believed to be mimicking the action of native bacterial DNA. Thus, the findings of Totte et al. are consistent with the claimed invention and provide evidence that one of ordinary skill in the art would recognize the immune response produced by CpG oligonucleotides as being representative of a response useful for the treatment of bacterial infection.

Bohn et al., Infection and Immunity, July 1994, v. 62, p. 3027-3032 is a study examining IFN-γ and other cytokines in mice infected with *yersinia enterocolitica*. The results obtained in this study supported the hypothesis that early and enhanced in vivo production of IFN-γ in response to the bacterial infection is associated with a state of heightened resistance against *Y. enterocolitica* infection. In the specification as filed Applicants have established that CpG oligonucleotides produce in vivo induction of IFN-γ. The findings of Bohn et al. are consistent with the specification

as filed and are supportive of Applicant's assertion that one of skill in the art would accept the correlation presented by Applicant that in vivo induction of cytokines would provide therapeutic effects against bacterial infection.

Autenrieth et al., Infection and Immunity, June 1994, v. 62, p. 2590-2599, describes a study examining induction of IFN-γ in mice and the ability of the mice to develop immunity to *Y. enterocolitica*. Use of antibodies to neutralize the induction of IFN-γ abrogated the resistance to infection in mice which had demonstrated an increase in the IFN-γ. The authors conclude that the results demonstrate the cellular immune response and in particular production of IFN-γ is associated with resistance of mice to *Y. enterocolitica*. Again, the reference is supportive of one of ordinary skill in the art at the time of the invention accepting the correlation between Applicants data and a therapeutic use for CpG oligonucleotides.

b. teachings related to Th1/Th2

Applicant addressed in detail the assertion that the claimed invention was unpredictable based on the papers cited in the office action teaching that the administration of cytokines was unpredictable. The examiner has not addressed any of these arguments specifically. The Examiner has reiterated that the cytokine art "demonstrates the unpredictability associated with the use of cytokine to treat a condition." Applicant does not believe that the Examiner has misunderstood the invention. The point that Applicant is making is that endogenous cytokine production is distinct from administration of exogenous cytokines. The administration of cytokines to a subject does not produce a balanced controlled response in the body. Endogenous induction of cytokines naturally in response to an inducing agent, however, maintains the natural balance and feedback systems that are critical to responding to invading microorganisms. A study relating to exogenous administration of cytokines does not translate directly to results achieved with endogenous induction of cytokines.

c. references submitted by applicant

In the previous response, Applicant provided references that demonstrate that the claimed invention can be predictably practiced by the skilled artisan by relying on the routine art. However,

according to the Examiner, the submitted references demonstrate that undue experimentation would be necessary to enable the claimed invention. Applicant address each of the Examiner's concerns.

The Examiner has interpreted Auricchio et al. as establishing that further characterization of the mechanism by which CpG indirectly promotes the killing of *M. Tuberculosis* is needed. However, the mere phrase "by which CpG indirectly promotes killing of *M. Tuberculosis*", as quoted by the Examiner, clearly shows that CpGs can be used to kill *M. Tuberculosis* and therefore can be used to treat a bacterial infection. In effect, the paragraph referenced by the Examiner (Page 918) states: "Our results demonstrate that CpG ODN induce human macrophages to kill intracellular MTB". The "further characterization of the mechanism" refers to the scientific question, if, in addition to cited mechanisms like TLR-2, other mediators may play a role in the killing of MTB. This question of further characterization does not render the teachings of Auricchio et al. unpredictable.

The Examiner has stated that the questioning of the mechanism of action by Auricchio et al. demonstrates that the skilled artisan cannot predictability use CpG in a manner that it is desirable. In the instant case Applicant has provided a teaching that a drug is useful for the therapeutic purpose of treating bacterial infection. Applicant has described the mechanism through which the drug is acting, i.e. induction of cytokines and a boosting of the immune response to an invading microorganism. The fact that many years later it is stated in a publication that the mechanism of action is unknown does not support the unpredictability of the claimed invention as of the priority date.

The Examiner quotes from Klinman, Conover and Coban: "There are only a limited number of settings in which such short term protection may be of therapeutic benefit." This quote is not evidence that the claimed invention does not work. In fact it implies that there is a "therapeutic benefit, the "short term protection" of these benefits refers back to earlier experiments (pre 1999) and in this (1999) publication, Klinman et al. show that "By repeatedly administering CpG ODN two to four times/month we found that this protection could be maintained indefinitely." Therapeutic regimes for the treatment of bacterial infection had therefore been established (Klinman et al. published in 1999).

Klinman, Conover and Coban describe therapeutic regimens for treating infection. The development of clinical regimens for the treatment of bacterial infection is within the skill of the ordinary artisan.

The Examiner also quotes from Raghavan et al. (p7021) "CpG oligonucleotides have no direct antibacterial effect". This quote misrepresents the findings of Raghavan et al. Indeed, the paragraph from which the quote is taken states: "We found that intragastic administration of CpG ODN without bacterial antigen codelivery results in a consistent reduction in the bacterial load in the stomachs of mice with established *H. pylori* infection. The ODN lacking CpG motifs had absolutely no protective efficacy, supporting the conclusion that the effects observed were mediated solely by the contextual CpG motif. Moreover, our in vitro studies indicated that CpG ODN has no direct antibacterial effect." This paragraph provides a teaching that CpG oligonucleotides provide a consistent reduction in bacterial load, and is supportive of the predictability of the art. The observation that CpGs have no direct antibacterial effect *in vitro* is not relevant. Applicant is not claiming a direct bactericidal effect. Rather, Applicant has taught that CpG influences the immune response in a manner that is useful for treating infection. In addition, the Examiner states that Raghavan et al. shows that reduction in the bacterial load occurred concomitant with both upregulation of RANTES production and rapid recruitment of immune cells, and that "no similar teachings can be found in Applicant's disclosure". However, Applicants disclosure page 52 reads: "In response to unmethylated CpG an increased number of spleen cells secrete .... RANTES." and "CpG DNA acts as an effective danger signal and causes the immune system to respond vigorously to new antigens in the area". The current application therefore teaches both the upregulation of RANTES and recruitment of immune cells, as observed by Raghavan et al. Regardless, Applicant asserts in the specification that CpG is useful for treating bacterial infection. Since the time of the invention, others have made consistent findings.

The Examiner has stated that the in vitro observation noted by Raghavan et al. demonstrates the unpredictability of the claimed invention because it shows that in vitro data do not support or correlate with in vivo data. Applicant disagrees. Raghavan et al. does not state that in vitro data does not support or correlate with in vivo data. Raghavan et al. simply points out that CpG ODN have no "direct antibacterial effect" in their in vitro studies. Raghavan et al. is not stating that the in

vitro studies don't correlate with their in vivo data. Rather, Raghavan is stating that the CpG does not have a direct antibacterial effect. Raghaven's in vivo data demonstrated a reduction in bacterial load as a result of CpG treatment, which presumably is an indirect effect due to immune factors themselves rather than a direct antibacterial effect.

When referring to Juffermans et al. the Examiner states that the protective immunity varies among IFN-gamma gene proficient and IFN-gamma deficient mice, and continues by noting that the claimed invention does not require a person to be proficient or deficient in a particular gene. It is not immediately clear to the Applicant how this argument reads on the predictability of the art and/or the enablement of the current claimed invention. Mice deficient in IFN-gamma genes are severely immunocompromised and are used as a research tool only, for instance to elucidate certain mechanisms. While the current application does not specifically mention that a person needs to be IFN gamma gene proficient, the absence of this statement does not preclude the enablement of the current claimed invention. A person of ordinary skill in the art would understand that most (if not all) subjects are IFN gamma gene proficient and would appreciate that in the rare case where a subject is not IFN gamma gene proficient a different treatment regime might apply. The Examiner also states that the application does not provide "any guidance or direction to establish the gene that the treatment must possess in order to benefit from the administration of a CpG". Applicant assumes that the Examiner is referring to genes that *subject* undergoing treatment must possess.

The Examiner has stated that the presence or absence of IFN-γ "speaks volume to the unpredictability of the claimed invention." and further that "the skilled artisan would not be able to effectively treat subjects that are interferon-γ deficient.". IFN-γ gene deficient subjects are not typical subjects. The mice described in the paper are animal models created to test a disease state. The fact that such animal models exist does not provide any teaching regarding the predictability of the claimed invention.

The Examiner continues the analysis of Juffermans et al. by stating that the claimed invention is directed at treating bacterial infection in a subject while Juffermans et al. is only teaching prevention of infection. However, Juffermans et al. is teaching the treatment of infection. As stated in the abstract: "CpG ODNs given 2 weeks after infection were still able to reduce mycobacterial outgrowth." which clearly pertains to treatment of a bacterial infection. The

Examiner also notes that Juffermans et al. discloses different treatment regimes for different bacteria. Differences in treatment regimens for different bacteria are part of the routine art. A person of ordinary skill in the art will appreciate that a rapidly replicating microorganism like *Lysteri monocytogenes* may require a different treatment regimen than the more indolent *Leishmania major*.

The Examiner has dismissed the teaching in Juffermans related to the use of CpG oligonucleotides to reduce micobacterial outgrowth as not being commensurate with the therapeutic efficacy of CpG oligonucleotides against bacterial infection. The reference teaches that CpG oligonucleotides given two weeks after infection were able to reduce micobacterial outgrowth. Such a teaching falls directly within the scope of the claimed invention. It is unclear why it is not commensurate with the therapeutic efficacy of CpG oligonucleotides against bacterial infection.

Krieg et al. echoes the findings of Juffermans et al., according to the Examiner, and also notes that different types of populations (as exemplified by IFN gamma deficient mice) may require different treatment regimens. Applicant's comments on this argument are noted above. The Examiner continues by stating that Krieg et al. found that excessive immune activation by CpG oligonucleotides may be deleterious and notes that the claims in the current application do not specify any amount other than "sufficient to treat bacterial infection". However, a person of ordinary skill can rely on the routine art to find treatment regimens that are effective, thereby avoiding excessive immune activation.

The Examiner has stated that based on the teachings of Kreig et al. one skilled in the art "would not be motivated to blindly administer any CpG oligonucleotide, at any dose, as suggested by the claimed invention, to activate an unknown/undefined immune response that treats bacterial infection." Applicant disagrees. The specification does not teach one skilled in the art to blindly administer any CpG oligonucleotide at any dose to activate an unknown immune response. The specification describes a class of compounds having common structural element of a CpG dinucleotide which can be administered to produce a specific immune response associated with the induction of certain cytokines as well as B-cell and NK-cell activation. Identification of a dose which is useful in human subjects can only be determined through clinical trials and does not require undue experimentation.

According to the Examiner, Hayashi et al. recognizes the use of CpG oligonucleotides as an adjuvant to the treatment of *M. avium* infection with the conventional antimicrobial agent clarihtromycin. Applicant acknowledges this observation, but also points out that Hayashi et al. also shows that "Treatment with a single dose of ISS-ODN (CpG) significantly decreased intracellular growth of *M. avium* in BMDMs by 68%, compared to the number of CFU in infected cells treated with M-ODN (control) or medium alone", thus describing a treatment regimen for bacterial infection using CpG, offering further evidence of the predictability of the art.

The Examiner has stated that "a reduction in bacterial growth, is not equivalent to the treatment of bacterial infection." Reducing or slowing the progression of a disease or infection is a useful treatment for a disease. A treatment for bacterial infection does not necessarily require complete removal of the infectious organism. Slowing of bacterial growth is a significant improvement that falls within the scope of the claims.

The Examiner continues the analysis of the references by quoting from Klinman, Verthelyi, Takeshita and Ishii on the risk of using CpG or DNA vaccines to stimulate innate or adaptive immunity. The Examiner quotes from page 126 where the authors enumerate potential problems with vaccination in general. However, the quoted paragraph concludes with " Balancing these safety concerns, toxicity has not been observed in normal animals injected with therapeutic doses of DNA vaccine or CpG ODN. In addition, none of the human volunteers exposed to DNA vaccines or anti-sense ODN have suffered serious adverse consequences." Thus, this paragraph shows that the routine art recognizes that the safety concerns in treatment with CpG oligonucleotides are not a major issue. Furthermore, the MPEP (§2164.01) states: "The applicant need not demonstrate that the invention is completely safe." In fact, one cannot possibly determine the parameters of safety without a controlled clinical trial, and it is well established that a clinical trial is not required for enablement. This is a regulatory issue that falls within a territory of the Food and Drug Administration.

Gursel et al. state that "The(se) immunostimulatory activities are being harnessed therapeutically", which the Examiner interprets as "The art is still trying to harness the immunostimulatory activities of CpG oligonucleotides to render therapeutic value". The teachings of Gursel et al. pertain to modifications of specific delivery methods resulting in an increase in

bioavailability, but does not reflect any unpredictability in the art. In effect, the teachings of Gursel et al. also reiterate the teachings on treatment of bacterial infections using CpG oligonucleotides in the routine art.

The Examiner has stated that if the art recognizes that immunostimulatory activities of CpG oligonucleotides are still being harnessed many years after the filing of the claimed invention that such a teaching supports unpredictability. Applicant disagrees. Even after FDA approved drugs continue to be tested and further properties are identified. It is not possible to know everything about a drug when a patent application is filed. The therapeutic potential of a drug leads it to be studied by many researchers. Because CpG oligonucleotides are such promising compounds for the treatment of infection and other diseases many researchers are studying their effects and will continue to make further discoveries. These discoveries do not support the unpredictability of the invention. Rather, the quantity of follow-on research related to CpG oligonucleotides and their use in treatment of infection supports the ground breaking discoveries made by Applicant.

Klinman and Kamstrup provide an overview of the state of the art in treating bacterial infections, by administration of CpGs. Their publication refers to the uses of CpGs as adjuvant, vaccine and therapeutic in infection subjects. For instance, on page 177, the authors refer to Zimmermann et al. (Zimmermann et al. 1998. J. Immunol.) who showed that a CpG protected susceptible mice from *leishmania* infection when administered several weeks after infection, which clearly shows that treatment of a bacterial infection with CpG was established in the routine art at the time of filing of the current application.

The final publication referred to by the Examiner is Elkins et al. Elkins et al. state that "the bacterial determinants that stimulate either inflammatory or lymphocyte dependent innate response are poorly understood." However, this quote is taken from the introduction of the publication, i.e. where the authors set out the scientific problem to be investigated. In the next paragraph, which summarizes their findings, the authors state that: "Here, we show that treatment of mice with either bacterial chromosomal DNA or oligonucleotide DNA containing unmethylated CpG motifs that stimulate Th-1 associated cytokine production, induces lymphocyte-dependent protection against lethal challenge with virulent *F. tularens* and *L. monocytogenes.*" The authors therefore provide an

understanding of the bacterial determinants that stimulate either inflammatory or lymphocyte-dependent immune response.

The Examiner has stated that the teaching of Elkins et al. describe the ability of CpG oligonucleotides to modulate infection by intracellular pathogens but does not refer to the therapeutic efficacy of CpG oligonucleotides to treat bacterial infection. The Examiner also states that Applicant admits the Elkins et al. reference predates the current application. Applicant acknowledges that such a statement was made. However, Applicant clarifies for the record that the statement previously made by Applicant was incorrect. Elkins et al. was published subsequent to the priority date of the instant application.

Finally, the Examiner has concluded that "the deficiency of the specification cannot further be contemplated by the teachings of the art. Applicants have not presented the data in the papers discussed above for purposes of enabling the claimed invention. The data is presented to rebut the rejection of record. The specification as filed provides adequate enablement for the claimed invention. The Examiner had asserted that the invention was unpredictable at the time of filing, as evidenced by teachings found in post-filing references. Applicants have asserted that one of skill in the art would have expected the invention to work as Applicants taught in the specification at the time the patent application was filed. The post-filing publications presented by Applicant demonstrate that the claimed methods actually do work as Applicant stated they would in the patent application. The teachings are consistent with the teachings and data described in the specification.

Rejections repeated from prior office action but not addressed:

As discussed above, the Examiner re-iterated the entire rejection under 35 USC 112 presented in the prior Office Action. Other than the specific points discussed above, the Examiner has not addressed any of Applicants' arguments filed in response to the Office Action. Thus, Applicants present arguments to address each of these rejections again.

State of the Art

The Examiner has made several statements about the state of the art. In order to address each statement, Applicants have copied the Examiner's statement and provide comments

immediately below.

- Cytokines have great potential for enhancing resistance against diverse pathogens; however, host response to exogenously administered cytokines can be dichotomous and may be dependent on the pathogenesis caused by the disease state.
    - The statement is not relevant to the claimed invention. Applicants are not exogenously administering cytokines. The claimed invention relates to the delivery of an oligonucleotide which stimulates in vivo the promotion or inhibition of cytokine production.
- Both Th1 and Th2 type of immune responses is necessary. Infante-Duarte et al. notes that it is important to produce enough of the Th1 type immune response to keep intracellular infection under control, while producing at the same time just enough of a Th2 type immune response to prevent the Th1 type immune response from causing damage to the host. In order to do so, a tight control over where and when Th1 and Th2 immune responses happen is necessary.
    - This teaching is not inconsistent with the claimed invention. The patent application teaches that CpG oligonucleotides promote an immune response when administered in vivo. The immune response involves a shift in the balance of Th1 and Th2 cytokines such that the Th1 response is favored. The shift is a natural one that occurs in response to a stimulus that Applicants believe a naturally existing stimulant, bacterial DNA. It is believed that CpG containing oligonucleotides mimic bacterial DNA in their ability to promote an immune response. The inventors believed they discovered one of natures pathways fundamental to the immune system. This discovery is described on pages 35-36 of the specification under the heading "Teleological Basis of Immunostimulatory Nucleic Acids." It is taught that the stimulatory CpG motif, identified according to the invention, is common in microbial genomic DNA, but quite rare in vertebrate DNA. Experiments described in Example 3, in which methylation of bacterial DNA with CpG methylase was found to abolish mitogenicity, demonstrated that the difference in CpG status is the cause of immune

stimulation by bacterial DNA. The resultant immune response is a natural one. Not one that is dramatically skewed to cause tissue damage.

- The efficacy of cytokines such as interleukin 2, interferon-gamma, and interleukin 18, remains controversial. For example, while interleukin 2 may confer good protection for non-pathogenic mycobacterial strain Bacille Calmette-Guerin (BCG), interleukin 2 does not confer protection for virulent *M. bovis* infection.
  - The statement is not relevant to the claimed invention. Applicants are not directly administering a cytokine. Additionally, the claimed invention relates to the delivery of an oligonucleotide which stimulates a pattern of cytokine production, not simply a single cytokine, such as IL-, IFN, or IL-18. Additionally, the Aoki et al reference cited by the examiner actually teaches that cytokines have promise in the treatment of infectious disease. On page 231 2nd column it is concluded that "Undoubtedly, in the next several years we may witness the formal introduction of cytokines or their inhibitors to routine clinical use for infectious diseases other than viral hepatitis." and "Cytokines hold great promise to be used as therapeutics or immune adjuvant for vaccination against infectious disease.....Several cytokines have been successfully used for human conditions and it is anticipated that more will enter into clinical applications."
- Interleukin-12, Th1 associated cytokine, induces different effector mechanisms that result in either protection or exacerbation. Bohn et al. teaches that the administration of exogenous interleukin 12 confers protection against Yersinia enterocolitica in susceptible BALB/c mice, but exacerbates yersiniosis in resistant C57BL/6 mice.
  - Again, the statement is not relevant to the claimed invention. Applicants are not directly administering a cytokine. Additionally, the claimed invention relates to the delivery of an oligonucleotide which stimulates a pattern of cytokine production, not simply a single cytokine such as IL-12.
- Interleukin 18, a Th1 associated cytokine, is responsible for the progression of endotoxin-induced liver injury in mice primed with interleukin 18.

- The statement is not relevant to the claimed invention. Applicants are not directly administering IL18. Administering a compound is very different than stimulating the body to produce the compound endogenously.

- Interleukin 6 and interferon gamma, both are Th1 associated cytokines, augment the susceptibility of monocyte-derived macrophages to infection with T-cell tropic CXCR4-utilitising HIV-1 strains; whereas, IFN-gamma inhibits viral entry and productive infection of mono-derived macrophages with macrophage-tropic HIV-1.
  - The statement is not relevant to the claimed invention. HIV is a virus. Applicants claims are limited to the treatment of bacterial infection.
- Interleukin 2, a Th1 associated cytokine, increases the production of HIV in vitro, and enhances the translocation of bacteria from intestines to other organs in animal studies. Additionally, the art also notes that a higher incidence of bacterial infections in AIDS patients receiving IL-2 treatment. (Office Action citing Masihi)
  - The statement is not relevant to the claimed invention. Applicants are not directly administering a cytokine. Administering a compound is very different than stimulating the body to produce the compound endogenously. This point is clarified in the Masihi reference itself. In his review article Masihi describes several classes of molecules and how they are used for fighting infection. One section (section 3) is on the exogenous administration of cytokines as therapeutic agents. This is the section cited by the Examiner which describes some of the troubles associated with exogenous administration of cytokines. The next section (section 4) describes synthetic and natural immunomodulators. Section 4.1 is dedicated to CpG oligonucleotides. Unlike all of the problems highlighted by Masihi related to cytokines, Masihi describes studies in which CpG ODN were demonstrated to protect against *Listeria moncytogenes* and *Francisella tularensis* in mice. Additionally studies are described relating to successful protection against *Trypansoma Cruzi* and *Leishmania major.* The author even concludes "CpG-ODN were even curative when given after lethal *Leishmania major* infection.: (page 647 1st full sentence).

- Interferon gamma is ineffective against the virulent strain of Mycobacterium avium. Silva et al. notes that the virulent strain resists the antimycobacterial activity of interferon-gamma.
- The statement is not relevant to the claimed invention. Applicants are not directly administering a cytokine. Administering a compound is very different than stimulating the body to produce the compound endogenously. Additionally the cited statement from the Silva reference is incorrect. On page 5583 last sentence left column Silva et al actually states that "virulent strains resist the antimycobacterial activity of *IFN-γ-activated macrophages*" (emphasis added.) IFN-γ-activated macrophages are different than IFN-γ.

Based on the above assertions, the Examiner concludes that "the art amply recognizes the following limitations: inherent toxicity of the material, their unclear pharmacological behavior, and their pleiotropic effects." None of the above-statements support the above conclusions. In each instance but one (the one referring to Infante-Duarte et al.) the Examiner is describing a system of one or more exogenously administered cytokines. Applicants have not claimed the administration of cytokines. Applicants claims are directed to the administration of oligonucleotides which produce a shift in the balance of cytokine production and cellular activation in a natural environment. The body controls how much of a particular cytokine to produce. The effect is different from administering cytokines. The ability to stimulate an immune response without directly administering immune factors such as cytokines is an advantage of the invention. The teachings of Infante-Duarte et al. cited by the Examiner are not inconsistent with the claimed invention and also don't support the above-conclusion.

Additionally, the Examiner has cited several teachings in the CpG art. Applicants addresses each of these below.

- The recognition of the CpG motifs requires Toll-like receptor (TLR) 9, wherein cells that express TLR-9 produce Th1 like proinflammatory cytokines, interferon and chemokines. However, the art also recognizes that TLR-9 is differentially expressed in human mice, and that TLR-9 has not been identified in species other than human and mice. Thus, with the variability of TLR-9 expression, including absence thereof,

the level of a Th-1 immune response would also be variable from one species of animals to the next. (Office Action, citing Mutwiri et al)

- Mutwiri et al actually state "TLR9 has yet to be identified in species other than human and mice, *but it is assumed that a similar signaling mechanism is involved in other species*". (Emphasis added) The Examiner's conclusion that the absence of TLR9 in some species would lead to variability in results is misplaced. The reference does not teach that TLR9 is absent is some species. Additionally the reference is a review article describing studies that have examined the effects of CpG therapies in a variety of animals, including mice, humans, cattle, sheep, pigs, horses, goats, rabbits, fish, dogs, cats, and chickens (see for instance page 90 first full paragraph of left column and first 20 lines of right column). The authors conclude in that paragraph in the right column of page 90 that "Together, these data suggest that in vitro stimulation of cells by CpG motifs is conserved across species, and that the enhanced activity of GACGTT in laboratory animals may be an artificial bias due to inbreeding."

- Every oligonucleotide containing the CpG motif must be considered as a separate agent because the quality and type of immune stimulation induced by these oligonucleotides varies. The art frequently notes that the specific nucleic acids, purines and pyrimidines, surrounding the CpG motif, influence both the level and type of immune stimulation; the spacings between CpG motifs surrounding the CpG motif influence both the level and type of immune stimulation; and the type of cytokine stimulated by oligonucleotides containing the CpG motif varies from one oligonucleotide to the next. The art also notes that variability occurs with different numbers of CpG motifs in an oligonucleotide, the absence or presence of a CpG motif to the end of the oligonucleotide, and the context in which the CpG motif is presented in the sequence.
  - Applicants have described a class of molecules (oligonucleotides) having a common structural motif (a CpG dinucleotide) that when administered to a subject results in an aspect of the immune response being altered, with a Th1 response being

favored. This class of oligonucleotides is described throughout the specification and their ability to produce a Th1 favored immune response and be used to treat disease is not only described (e.g., see page 8, lines 5-16 and page 40-42) but data is presented *in vitro* and *in vivo* using an adequate number of different CpG containing oligonucleotides to meet the enablement requirement for the claimed invention. The fact that there is some variability in the responses depending on the sequence of the oligonucleotide is not surprising. If one were proceeding in a clinical trial one would have to select a single oligonucleotide to use. However, this is not the standard for enablement. Variability with drugs in humans is not unusual. Humans are an outbred population, genetically diverse, and humans respond with great variability to drugs. This is particularly the case where the immune system is involved. Humans have an immune status that fluctuates much more than the mice used in experimental research. A human's immune status on any particular day can determine the human's response to a drug.

- In vitro observations do not accurately predict what happens in vivo. (Office Action, citing Mutwiri et al)
  - The cited statement is true for any biological agent. A regulatory authority such as the FDA would not approve a drug simply on the basis of in vitro tests. However, this is not the standard for patentability. The statement is not specific and has no bearing on the enablement of the claims.
- The immunostimulatory activity of CpG oligonucleotides is species specific. The human CpG motif, GTCGTT, is optimal for stimulation of lymphocyte proliferation in several species including cattle, sheep, goats, horses, pigs, dogs, cats and chickens. And the murine CpG motif (GACGTT) is only optimal for inbred rabbits and mice. (Office Action, citing Mutwiri et al)
  - The statement does not provide support for lack of enablement. Simply because one embodiment might be optimal or preferred does not make other embodiments non-enabled. Additionally, the statement taken from Mutwiri et al reflects the analysis of

data from several published articles. It does not purport to analyze each and every CpG ODN.

- The immunomodulatory effect induced by oligonucleotides containing the CpG motif varies from one species to another. (Office Action, citing Mutwiri et al)
  - As described above, variability is expected. However, it has been described in the specification and confirmed in numerous references that CpG containing oligonucleotides stimulate an immune response. The consistent effect is attributed to the presence of the unmethylated CpG motif in the oligonucleotide.
- Oligonucleotides containing the CpG motif increase the susceptibility to infection by *Candida albicans*. Ito et al. notes that although oligonucleotides containing the CpG motif promote Th1 immunity, the induction of IL-12 by the oligonucleotide increases infection by *Candida albicans* in mice, rather that protecting the mice from said infection. (Office Action, citing Ito et al)
  - *Candida albicans* is a yeast, not a bacteria. The claimed invention is directed to the treatment of bacterial infection using CpG oligonucleotides. Ito et al states that CpG ODN "treatment typically improves host resistance to infection by bacterial, viral, and parasitic pathogens." (page 6154, left column, first paragraph last sentence)

Thus, none of the references or passages cited by the Examiner support a conclusion of the lack of enablement of the claimed invention.

Presence or absence of working examples:

The Examiner has stated that the "specification does not contain any working examples suggesting or demonstrating that the administration of an oligonucleotide containing the CpG motif is effective in treating bacterial infection....All that is present in the specification are working examples directed at measuring the effect of various structural manipulations of oligonucleotides containing the CpG motif."

Applicants have taught that in addition to induction of IFN-gamma the working examples in the specification show production of antibody in response to oligonucleotide stimulation (Example 2), stimulation of B cells, natural killer (NK) cells and monocytic cells (Example 3, Example 4,

Example 11, Figure 6 and Figure 11), and production of IFNγ (Figure 15) as well as other cytokines. The specification asserts that CpG oligonucleotides are useful in treating bacterial infections. The combination of the changes in immune parameters demonstrated with CpG oligonucleotides is sufficient to support applicants assertion at the time of the invention that CpG oligonucleotides would be useful in the treatment of bacterial infection. Applicants assert that a correlation between CpG and their use in the treatment and/or prevention of bacterial infection is disclosed and enabled.

Amount of direction or guidance presented:

Applicants have provided sufficient direction and guidance in the specification. Applicant has described the structural properties of CpG oligonucleotides and have taught that they can be used to treat bacterial infection. Further applicants have provides preferred modes of administration and formulations. Those of skill in the art are well aware of such routine methods of formulating and administering drugs.

Predictability or unpredictability of the art:

The Examiner has stated that "As demonstrated by Applicant in the disclosure and the teachings in the art, the use of oligonucleotides containing CpG motif is unpredictable." Applicants disagree. Applicant has addressed each statement by the Examiner from the prior art which was put forth to support this conclusion of lack of predictability. There is no evidence of unpredictability of the invention. The variability observed with CpG oligonucleotides is not sufficient to demonstrate unpredictability. It simply shows that some oligonucleotides work better than others at stimulating the immune response. Applicants have identified the key structural property , the unmethylated CpG dinucleotide, that allows this class of oligonucleotides to function through TLR9 to stimulate an immune response that is useful in the treatment of bacterial infection.

Quantity of experimentation necessary:

The Examiner has provided several reasons for why additional experimentation would be necessary. For instance it is stated in the Office Action that "Applicant has not provided any

guidance relating to how the immunostimulatory activities observed for several oligonucleotides containing CpG motif translates to the treatment of bacterial infections...pertaining to the type of activity that would need to be stimulated to provide effective treatment against bacterial infections....relating to the level of immune stimulation that would be required to provide effective treatment against bacterial infections." It is unclear how any of these factors relate to extensive experimentation. Applicants have taught how to make the CpG ODNs using routine methods known in the art. Applicants have also taught that they produce a pattern of immune stimulation and that they can be administered for the treatment of bacterial infection. One of skill in the art would simply need to make the ODN or buy it and administer it to a subject having a bacterial infection. The skilled artisan would know the best routes of administration to use depending on the infectious agent and the subject.

In view of the teaching of the instant application and the state of the art at the time of filing, Applicants submit that the claimed invention can be practiced without undue experimentation. Applicants have provided CpG oligonucleotide sequences that stimulate an immune response (and demonstrated a number of immune parameters *in vivo* and *in vitro*) and have provided guidance to one of ordinary skill in the art to use the CpG oligonucleotides to treat or prevent a bacterial infection. Based on the teachings in the specification one skilled in the art would have predicted that CpG is capable of treating bacterial infection. Numerous references, including those cited by the Examiner, have shown that CpG oligonucleotides can overcome infection, suggesting that CpG ODN is effective in treating bacterial infection. Therefore, the amount of experimentation required to practice the invention is not undue.

Accordingly, withdrawal of the enablement rejection under 35 U.S.C. §112 is respectfully requested.

Double Patenting Rejection

Claim 104 has been provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claim 30 of copending Application No. 10/735592. Claim 30 of US 10/735592 has been withdrawn from consideration and is no longer pending. Thus, it is requested that the rejection be withdrawn.

Claim 104 has been provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claim 41 of copending Application No. 10/894682. Application No. 10/894682 is not filed by Applicant of the current application. Applicant assumes that the Examiner is referring to Application No. 10/894862. Claim 41 of US 10/894862 has been withdrawn from consideration and is no longer pending. Thus, it is requested that the rejection be withdrawn.

Claim 104 has been provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claim 67 of copending Application No. 10/224523. Claim 37 of US 10/224523 has been withdrawn from consideration and is no longer pending. Thus, it is requested that the rejection be withdrawn.

Claim 104 has been provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claim 19 of copending Application No. 10/613916. The rejection is a provisional one since none of the claims in the 10/613916 application have been found allowable. Applicants defer substantive rebuttal until the above-identified claims are allowed.

Claim 104 has been provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claim 38 of copending Application No. 10/787737. The rejection is a provisional one since none of the claims in the 10/787737 application have been found allowable. Applicants defer substantive rebuttal until the above-identified claims are allowed.

CONCLUSION

A Notice of Allowance is respectfully requested. The Examiner is requested to call the undersigned at the telephone number listed below if this communication does not place the case in condition for allowance.

If this response is not considered timely filed and if a request for an extension of time is otherwise absent, Applicant hereby requests any necessary extension of time. If there is a fee occasioned by this response, including an extension fee, that is not covered by an enclosed check, please charge any deficiency to Deposit Account No. 23/2825.

Dated: December 12, 2007

Respectfully submitted,

By _____

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